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Use of selected cephalosporins in penicillin-allergic patients: a paradigm shift

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Abstract

Recent analysis of clinical data and a clearer understanding of the role of chemical structure in the development of cross-reactivity indicate that the increased risk of an allergic reaction to certain cephalosporins in penicillin-allergic patients is smaller than previously postulated. Medline and EMBASE databases were searched using the following keywords: *cephalosporin*, *penicillin*, *allergy*, and *cross-sensitivity* for the years 1960 to 2005. Among 219 articles retrieved, 106 served as source material for this review. A significant increase in allergic reactions to cephalothin, cephaloridine, cephalexin, cefazolin, and cefamandole was observed in penicillin-allergic patients; no increase was observed with cefprozil, cefuroxime, ceftazidime, or ceftriaxone. Clinical challenges, skin testing, and monoclonal antibody studies point to the paramount importance of similarities in side chain structure to predict cross-allergy between cephalosporins and penicillins. First-generation cephalosporins have a modest cross-allergy with penicillins, but cross-allergy is negligible with 2nd- and 3rd-generation cephalosporins. Particular emphasis is placed on the role of chemical structure in determining the risk of cross-reactivity between specific agents.

Keywords: Cephalosporin; Penicillin; Chemical structure; Cross reactivity; Penicillin-allergy; Cefdinir; Cefpodoxime; Cefuroxime; Cephaloridine; Cephalexin; Cephalothin; Cefazolin; Cefamandole

1. Introduction

For some time, it has been widely believed that cephalosporins, because of similarities in their β-lactam ring structures, cross-react with penicillins and therefore should not be given to patients known to be penicillin allergic. However, opinion is changing because penicillin allergy is better defined and clinicians better understand the roles of chemical structure on the likelihood of cross-reactivity.

Recently, the American Academy of Pediatrics practice guidelines for the management of acute bacterial sinusitis and acute otitis media endorsed the use of specific cephalosporin antibiotics (cefdinir, cefpodoxime, ceftriaxone, and cefuroxime) for patients with reported allergies to penicillin, provided that the penicillin reaction is not severe (anaphylaxis) (American Academy of Pediatrics and American Academy of Family Physicians, 2004) or of a "type I" allergy (American Academy of Pediatrics, 2001). Although the published guidelines for the management of acute bacterial sinusitis preclude use of cephalosporins in patients with a "type I" allergy to penicillin, this recommendation is intended to apply only to those patients with a severe reaction. It is recommended that patients with a "non-type I" allergic reaction to penicillin can receive cephalosporins (American Academy of Pediatrics and American Academy of Family Physicians, 2004) because reactions to these agents do not have an allergic foundation and are usually idiopathic. The *Sinus and Allergy Health Partnership* guidelines for acute bacterial rhinosinusitis also support the use of the above cephalosporins in patients with nonserious allergic reactions to penicillins (Anon et al., 2004).

This article provides an overview of the data supporting these evidence-based guidelines that show a lack of cross-reactivity between most 2nd- and 3rd-generation cephalosporins and penicillins. Particular emphasis is placed on the role of chemical structure in determining the risk of cross-reactivity between specific agents.

2. Why the paradigm shift

It is increasingly being recognized that the cited rate of cross-sensitivity to cephalosporins among penicillin-allergic

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patients (about 10%) is an overestimate (Pichichero, 2005). This rate is based on data collected and reviewed during the 1960s and 1970s (Dash, 1975; Kabins et al., 1965; Petz, 1971, 1978; Scholand et al., 1968; Thoburn et al., 1966) and from results of in vitro tests (Assem and Vickers, 1974; Crieco, 1967; Girard, 1968) that were not supported by clinical skin tests in penicillin-sensitive patients (Stewart, 1962)

2.1. Early reviews of cross-reactivity

The reviews of Dash (1975) and Petz (1971; 1978), which respectively reported allergic reactions to cephalosporins in 7.7% and 8.1% of "penicillin-allergic" patients (allergy was based on patient history), included the 1st-generation agents cephaloridine, cephalexin, cephalothin, and cefazolin, and the 2nd-generation agent cefamandole. Reported rates of allergy were 0.9% and 1.9%, respectively, in patients without a history of penicillin allergy. These latter rates possibly estimate the risk of a primary cephalosporin allergy and are not considered in most publications that quote 10% as the rounded rate of allergic reactions to cephalosporins in penicillin-allergic patients. Further compounding the issue, Dash (1975) and Petz (1971; 1978) overestimated the number of patients with cross-sensitivity for a number of reasons. Dash did not consider the observation that there is a coincidental 3-fold increased risk of adverse reactions to any unrelated drugs in penicillin-allergic patients (Smith et al., 1966), and he only loosely defined allergy, including reports of patients with unspecified rashes in his analyses. More importantly, before 1980, 1st-generation cephalosporins were produced by the *Cephalosporium* spp. mold and were shown to be contaminated with trace amounts of penicillin (Saxon et al., 1987). Currently available cephalosporins do not have this contamination.

Much of the confusion regarding cephalosporin allergy in penicillin-allergic patients is caused by the uncritical application of the term "allergic reaction" to any adverse reaction occurring in patients receiving these agents (Saxon et al., 1987), and use of the phrase "clinically relevant cross-sensitivity" when any cross-reactive antibody is detected. In everyday practice and in many epidemiologic surveys, patients with histories of penicillin or cephalosporin "allergy" have actually had nonimmunologic drug-related side effects such as vomiting, diarrhea, and nonspecific rash; idiopathic reactions; or temporally related adverse experiences that were inappropriately attributed to the drug. Immunoglobulin (Ig) E-mediated reactions (type I, immediate hypersensitivity reactions) are the only true allergic reactions (Gell and Coombs, 1963), and it is these reactions that should be considered when determining the likely risk of cross-reactivity to cephalosporins in penicillin-allergic patients. Type II reactions mediated by IgG antibodies and type III reactions mediated by IgG or IgM antibodies are not allergic reactions. In fact, most patients develop IgG and IgM antibodies after receiving penicillin and show no adverse consequences (Petz, 1971). Although these antibodies may cross-react with cephalosporin antigens in in vitro assays (Anderson, 1986; Anne and Reisman, 1995; Batchelor et al., 1966; Levine, 1973; Levine et al., 1966; Saxon et al., 1987; Torres et al., 1997), these tests are not predictive of immunologic cross-allergy.

2.2. Treatment options for penicillin-allergic patients

A further reason for the recent reassessment of the use of cephalosporins in penicillin-allergic patients is the paucity of alternative antibacterials for these patients. Until the early 1990s, pneumococcal respiratory tract infections in penicillin-allergic patients were readily treated with macrolides (Doern, 2001). Resistance rates, however, along with clinical failure rates to these agents have recently increased dramatically (Dagan et al., 2000b; Doern, 2001). In fact, the macrolides and azalides have limited efficacy against both *Haemophilus influenzae* and *Streptococcus pneumoniae* (Anon et al., 2004; Dagan et al., 2000a, 2000b). Lincosamides, tetracyclines, rifamycins, and folate inhibitors are also of limited usefulness because of concerns over their efficacy against *H. influenzae* and other major respiratory pathogens, the risk of rapidly developing resistance, or current resistance rates. When used, many of these agents are associated with bacteriologic failure rates of 20% to 25% (Anon et al., 2004).

3. The real risk of cephalosporin cross-reactivity in penicillin-allergic patients

3.1. Effect of chemical structure on the risk of cross-reactivity

Penicillins and cephalosporins have a number of similarities in their chemical structures. They are of low molecular weight, are highly substituted in their side chains, and possess a β-lactam ring on which antimicrobial activity depends in addition to a separate ring structure containing sulfur (Hewitt, 1973). However, important structural differences exist in that the sulfur ring is a 5-membered thiazolidine ring in penicillins and a 6-membered dihydrothiazine ring in cephalosporins. The cephalosporin structure is less asymmetric than that of penicillins, and cephalosporins have 3 sites for substitution, whereas penicillins have only 2 (Hewitt, 1973). They also differ in their degradation pattern. The β-lactam ring of penicillins spontaneously opens under physiologic conditions and forms the stable penicilloyl group with preservation of the thiazolidine ring (the penicilloyl group acid is the major antigenic determinant); subsequently, they develop haptens capable of forming protein conjugates. Cephalosporins undergo rapid fragmentation of the β-lactam and dihydrothiazine rings, and the resultant compounds are extremely unstable and rapidly form simple degradation products that do not function as haptens (Hewitt, 1973; Marks and Garrett, 1970; Mayorga et al., 2002; Romano et al., 2004; Walter

Table 1
Metaanalysis of cephalosporin and penicillin cross-allergy based on penicillin allergy history

Comparison	Studies	No. of patients	Statistical method	Effect size
1st generation				
Cephalothin	2	1353	OR, 95% CI	2.50 [1.13–5.52)
Cephaloridine	2	15 702	OR, 95% CI	8.74 (5.95–12.84)
Cephalexin	2	14 752	OR, 95% CI	5.78 (3.62–9.21)
All 1st-generation cephalosporins	8	33 742	OR, 95% CI	4.79 (3.71–6.17)
2nd generation				
All 2nd-generation cephalosporins	2	7335	OR, 95% CI	1.13 (0.61–2.12)
3rd generation				
All 3rd-generation cephalosporins	2	6207	OR, 95% CI	0.45 (0.18–1.13)
All generation of cephalosporins	12	47 284	OR, 95% CI	2.63 (2.11–3.28)
2nd- and 3rd-generation cephalosporins	4	14 442	OR, 95% CI	0.85 (0.51–1.42)

et al., 1999; Warrington and McPhillips, 1996; Weiss and Adkinson, 1988). Therefore, on the basis of these differences in chemical structure and degradation, immunologic cross-reactivity between the β-lactam rings of these compounds should be minimal.

3.2. Studies evaluating cephalosporin allergy in penicillin-allergic patients

Recent evaluation of published clinical studies indicates that, in most instances, there is no reason for concern regarding cross-reactivity between cephalosporins and penicillins. Analysis of pooled data from 23 studies (Anne and Reisman, 1995; Apicella et al., 1966; Assem and Vickers, 1974; Audicana et al., 1994; Blanca et al., 1989; Dash, 1975; Griffith and Black, 1964; Lin, 1992; Martin et al., 1992; Miranda et al., 1996; Novalbos et al., 2001; Petz, 1978; Pichichero and Pichichero, 1997; Sastre et al., 1996; Saxon et al., 1987; Shepherd and Burton, 1993; Solley et al., 1982; Stewart, 1962; Sullivan et al., 1981; Thoburn et al., 1966; Walters et al., 1963; Warrington et al., 1978; Weinstein et al., 1964) with approximately 2400 patients with a reported history of penicillin allergy and about 39 000 patients with no such history showed that the risk of cross-reactivity was related to side chain configuration and correspondingly to cephalosporin generation (Pichichero, 2005). In these 23 studies, about 2200 patients had the presence of penicillin allergy evaluated by skin testing (Pichichero, 2005). The 1st-generation cephalosporins included in the evaluation generally share a chemical side chain similar to penicillin or amoxicillin. Analysis showed that the attributable risk of an allergic reaction to cephalosporins in penicillin-allergic patients was increased by about 0.5% with the 1st-generation agents ($P < 0.0001$). In calculating attributable risk, the 3-fold increased risk of allergic reactions in penicillin-allergic patients to nonrelated drugs is taken into consideration (Smith et al., 1966). Second- and 3rd-generation cephalosporins generally have different side chains from penicillin and amoxicillin, and these agents were not associated with any increased risk of cross-reactivity with penicillin; cross-reactivity rates ranged from −0.8% to 0.2% (Pichichero, 2005). There was also no increased risk of anaphylaxis to cephalosporins in penicillin-allergic patients (Pichichero, 2005).

Although the shared β-lactam ring of penicillins and cephalosporins is not predictive of cross-reactivity, a considerable body of evidence has established that cross-reactivity between different cephalosporins and between cephalosporins and penicillins is dependent on the side chain structure of these agents (Anne and Reisman, 1995; Audicana et al., 1994; Baldo, 1999; Baumgart and Baldo, 2002; Blanca et al., 1989, 1994; Hamilton-Miller and Abraham, 1971; Marcos Bravo et al., 1995; Marks and Garrett, 1970; Martin et al., 1992; Miranda et al., 1996; Romano et al., 2000a, 2004; Saxon et al., 1987; Silviu-Dan et al., 1993; Walter et al., 1999; Warrington and McPhillips, 1996). A summary of the findings of clinical studies evaluating cephalosporin cross-reactivity in penicillin-allergic patients according to the likelihood of cross-reactivity is presented in Tables 1 and 2. For most 1st-generation cephalosporins with a side chain similar to that of penicillin/amoxicillin, the risk of cross-reactivity is increased. However, for later-generation cephalosporins with side chains that differ from those of penicillin/amoxicillin, there is no increased risk of cross-reactivity. Examples of cephalosporins that might be expected to be associated with an increased risk of cross-reactivity to penicillins include cephalothin and cephaloridine that have identical thiophene

Table 2
Metaanalysis of cephalosporin and penicillin cross-allergy based on penicillin skin testing confirming penicillin allergy

Comparison	Studies	No. of patients	Statistical method	Effect size
1st generation				
All 1st-generation cephalosporins	2	115	OR, 95% CI	4.13 (0.70–24.51)
2nd generation				
All 2nd-generation cephalosporins	2	685	OR, 95% CI	1.13 (0.33–5.40)
3rd generation				
All 3rd-generation cephalosporins	1	685	OR, 95% CI	0.75 (0.15–3.66)
All generation of cephalosporins	7	1831	OR, 95% CI	1.44 (0.65–3.19)
2nd- and 3rd-generation cephalosporins	3	1370	OR, 95% CI	1.02 (0.36–2.88)

Table 3
Cross-reactivity between penicillins and cephalosporins based on side chain similarity

7-Position side chain						
Similar side chain/ cross-reactivity possible within group[a,b]	Similar side chain/ cross-reactivity possible with group	Similar side chain/ cross-reactivity possible with group	Completely dissimilar side chains/unlikely cross-reactivity with each other[b,c]			
Cephaloridine(1st) Cephalothin (1st) Penicillin G	Cefaclor (2nd) Cephradine (1st) Cephalexin (1st) Cefadroxil (1st) Amoxicillin Ampicillin	Cefepime (4th) Ceftizoxime (3rd) Cefpirome (4th) Cefotaxime (3rd) Cefpodoxime (3rd) Ceftriaxone (3rd)	Cefoperazone (3rd) Cefotetan (2nd) Cefazolin (1st) Cefuroxime (2nd) Cefdinir (3rd) Cefditoren (3rd)	Cefixime (3rd) Cefprozil (2nd) Cefmetazole (2nd) Ceftibuten (3rd) Ceftazidime (3rd) Cefoxitin (2nd)		
3-Position side chain						
Similar side chain/ cross-reactivity possible within group[b,d]	Similar side chain/ cross-reactivity possible within group	Similar Side chain/ cross-reactivity possible within group	Similar side chain/ cross-reactivity possible within group	Similar side chain/ cross-reactivity possible within group	Similar side chain/ cross-reactivity possible within group	Dissimilar side chain/unlikely cross-reactivity with each other[b,e]
Cefadroxil (1st) Cephalexin (1st)	Cefmetazole (2nd) Cefoperazone (3rd) Cefotetan (2nd)	Cefotaxime (3rd) Cephalothin (1st)	Ceftibuten (3rd) Ceftizoxime (3rd)	Cefuroxime (2nd) Cefoxitin (2nd)	Cefdinir (3rd) Cefixime (3rd)	Cefpodoxime (3rd) Cefprozil (2nd) Ceftibuten (3rd) Ceftriaxone (3rd) Cefepime (4th) Cefpirome (4th) Cefazolin (1st) Cefaclor (2nd) Ceftazidime (3rd)

[a] Based on the 7-position side chain structure similarity, allergic cross-reactivity might occur among these 3 drugs: cephaloridine (2nd-generation cephalosporin), cephalothin (1st-generation cephalosporin), and penicillin. The same interpretation applies to subsequent 4 columns.

[b] To apply this table clinically, check the antibiotic for cross-reactivity possibilities based on both the 7-position and 3-position side chains. If either side chain position is shared between antibiotics to avoid a possible cross-allergy reaction to be considered, such use would not be recommended. If neither of the side chains shares structured similarity between antibiotics, then cross-reactivity is highly unlikely and such antibiotics can be recommended without anticipated increased risk of a cross-allergy reaction.

[c] Based on the 7-position side chain structure uniqueness, allergic cross-reactivity would be highly unlikely for all of these cephalosporins with each other and with all other cephalosporins as well as penicillins.

[d] Based on the 3-position side chain structure similarity, allergic cross-reactivity might occur between these 2 drugs: cefadroxil (1st-generation cephalosporin) and cephalexin (1st-generation cephalosporin). The same interpretation applies to the subsequent 6 columns.

[e] Based on the 3-position side chain structure uniqueness, allergic cross-reactivity would be highly unlikely for all these cephalosporins with each other and with all other cephalosporins as well as penicillins.

2-acetic acid side chains that closely resemble the phenylacetic acid side chain of benzylpenicillin, and cefaclor, cephradine, cephalexin, and cefadroxil, that have side chains with similarities to those of ampicillin and amoxicillin (Table 3).

3.3. Monoclonal antibody studies

The role of chemical structure in cross-reactivity between cephalosporins and penicillins is also demonstrated in monoclonal antibody analyses. Mayorga et al. (1995) evaluated the antigenic contribution of different regions of the penicillin molecule by raising monoclonal antibodies against amoxicillin–protein conjugates. Eleven of 12 monoclonal antibodies (92%) recognized an epitope in which the side chain was a major constituent (although with variable contributions from other regions of the molecule); none recognized the thiazolidine ring or the conjugated nuclear region, and 1 recognized all different structures of the penicillin molecule equally. In a study of monoclonal antibodies against cephalexin in mice, Nagakura et al. (1990) found that degradation products and side chain components influenced cross-reactivity between penicillins and cephalosporins. Virtually, no cross-reactive epitopes between penicillins and cephalosporins were identified, however, supporting a lack of immunologic cross-reactivity between these agents.

3.4. Role of skin testing

Penicillin skin testing does not reliably predict cephalosporin allergy unless the side chain of the penicillin or ampicillin reagent is similar to the side chain of the cephalosporin under evaluation (Pichichero, 2005). Thus, studies using skin testing to determine cross-reactivity between penicillins and cephalosporins generally show some cross-reactivity between penicillins and cephalothin and cephaloridine, and between ampicillin/amoxicillin and cephalexin/cefadroxil, but not between penicillin/amoxicillin and later-generation cephalosporins (Assem and Vickers,

1974; Audicana et al., 1994; Crieco, 1967; Girard, 1968; Igea et al., 1992; Martin et al., 1992; Miranda et al., 1996; Novalbos et al., 2001; Romano et al., 2000b; Romano et al., 1998; Saenz de San Pedro et al., 2002; Solley et al., 1982; Thoburn et al., 1966). Nevertheless, radioallergosorbent tests (RAST) or skin testing showing the presence of a potentially cross-reactive IgE antibody to penicillin or cephalosporins are not anywhere near fully predictive of a clinical reaction. In clinical studies using RAST or skin testing, most patients (about 90%) with documented IgE antibodies to penicillin or amoxicillin tolerated cephalosporins with identical or very similar side chains to the penicillin responsible for the allergy (Blanca et al., 1989; Sastre et al., 1996).

Results of studies examining IgE responses in patients with immediate allergic reactions to cephalosporins indicated that fewer than 20% reacted on skin testing to classic determinants of penicillins (penicillin G, amoxicillin, and ampicillin), but most had positive results to other cephalosporins with the same or similar side chain structures to the cephalosporin responsible for the allergy (Romano et al., 1998, 1999, 2000a, 2000b).

The value of penicillin skin testing for predicting an allergy to cephalosporins in patients with a history of penicillin allergy is therefore controversial. If the penicillin or amoxicillin side chain is identical or similar to that of the cephalosporin being used, such testing is of possible value. Cephalosporin skin testing may also be useful in detecting IgE antibodies to the specific agent used in testing and other cephalosporins with similar side chains.

4. Conclusions

In clinical practice, many patients who present with a history of penicillin allergy have not had an immunologic reaction to a penicillin. In patients with a documented IgE-mediated reaction to a penicillin, use of cephalosporins with a similar side chain should be avoided. However, cephalosporins with different side chains may be given, particularly if the allergic reaction was not severe. These recommendations are based on the results of systematic review of the available literature and an understanding of the role of chemical structure in the pathogenesis of cross-reactivity.

Evidence indicates that the incidence of cross-reactivity with cephalosporins in penicillin-allergic patients varies with the chemical side chain similarity of the cephalosporin to penicillin or amoxicillin. All 1st-generation cephalosporins have the potential for cross-reactivity, but the risk is less than the 10% rate that has been presumed. In fact, the attributable risk is closer to 0.5% (Pichichero, 2005). Most 2nd- or 3rd-generation cephalosporins, particularly those endorsed by the American Academy of Pediatrics for sinusitis (American Academy of Pediatrics, 2001) and otitis media (American Academy of Pediatrics and American Academy of Family Physicians, 2004), and the Sinus and Allergy Health Partnership (Anon et al., 2004) (cefuroxime, cefpodoxime, ceftriaxone, and cefdinir), are highly unlikely to be associated with cross-reactivity based on differences in their chemical structure compared with penicillins and early cephalosporins.

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